REMARKS

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

I. Restriction requirement/election

Election, with traverse, of the claims of Group II (encompassing claims 2-12 and 21-26), directed to antibodies which specifically bind to polypeptides of SEQ ID NO:1 (including variants and fragments of SEQ ID NO:1), compositions thereof, and methods of making the antibodies, is acknowledged.

Claims directed to methods of using the antibodies for detecting polypeptides specifically bound by the antibodies (i.e., claim 13), and for purifying polypeptides specifically bound by the antibodies (i.e., claim 14), could and should be examined together with the product claims from which they depend, per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants presume that these method claims will be rejoined, upon determining allowability of the product claims from which they depend.

II. Priority

Claims 4, 6-9, and 21-23 were denied the benefit of the filing dates of parent applications 09/206,499 and 08/828,242 because the subject matter of the claims is allegedly not disclosed in these earlier filed applications "so as to have meet the requirements set forth under 35 USC § 112, first paragraph" (Office Action, July 24, 2003; page 5, § 6). The denial of priority is traversed.

With respect to claim 4, the Office Action asserts that "the originally filed disclosure of US Application No. 09/206,499 does not include an adequate description of the broad genus of acceptable excipients. Rather US Application No. 09/206,499 merely discloses, 'pharmaceutical

compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients' (column 20); and in this particular context, also discloses examples of 'suitable excipients' (column 20)" (Office Action, July 24, 2003; pages 5-6). However, compositions comprising an antibody and an acceptable excipient **are** adequately supported by the disclosure of the parent applications, U.S. application 09/206,499 and U.S. application 08/828,242.

Nevertheless, to expedite prosecution, claim 4 has been amended such that the recited compositions comprise an antibody "and an excipient." Support for this amendment can be found in the specification at, for example, page 27, line 26 to page 28, line 1. By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include compositions comprising an antibody and "an acceptable excipient." Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claim 4, as amended, recites patentable subject matter. The disclosure of U.S. applications 09/206,499 and 08/828,242 contains an adequate written description of the claimed subject matter, and claim 4, as amended, is entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997).

With respect to claims 6-9, the Office Action asserts that "the claims recite method steps, which do not appear to be particularly described in the originally filed disclosure of US Application No. 09/206,499" (Office Action, July 24, 2003; page 6). However, the recited method steps of claims 6 and 8 **are** adequately supported by the disclosure of the parent applications, U.S. application 09/206,499 and U.S. application 08/828,242.

In determining whether there is adequate support in the specification to convey to a skilled artisan that the inventors had possession of the claimed invention, the M.P.E.P. provides that "[t]he subject matter of the claim need not be describe literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." M.P.E.P. § 2163.02. Thus, there is no requirement for the specification to literally recite each of the steps of the recited method claims. All

that is required is that the specification **reasonably** conveys that the inventors were in possession of the claimed invention.

Furthermore, the M.P.E.P. provides that:

> To comply with the written description requirement of 35 U.S.C. 112, para. 1, or to be entitled to an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c), each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. When an explicit limitation in a claim 'is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation.' *Hyatt v. Boone*, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998). M.P.E.P. § 2163 at subsection II.3.(b)

Thus, there is no requirement that each step of the methods recited by claims 6 and 8 be literally described in the specification as long as a skilled artisan would reasonably understand that the inventors were in possession of the claimed invention.

Moreover:

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating 'the description need not be in *ipsis verbis* [i.e., 'in the same words'] to be sufficient'). M.P.E.P. § 2163 at subsection II.3.(a)

Therefore, an adequate written description does not require a detailed description of "[w]hat is conventional or well known" in the art. For example, since methods of preparing polyclonal and/or monoclonal antibodies are well known in the art, the explicit recitation of each of the steps of claim 6 and/or 8 is not required in order for the specification to provide an adequate written description of these claims. For at least these reasons, the disclosure of U.S. applications 09/206,499 and 08/828,242 contains an adequate written description of the claimed subject matter, and claims 6-9 are entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997).

In regards to claims 6 and 7, step a) of claim 6 is described in the specification at, for example, page 23, lines 10-24; and page 42, lines 16-17. Step c) of claim 6 is described in the specification at, for example, page 24, lines 20-26; and page 42, lines 17-20. Step b) of claim 6, which recites "isolating antibodies from the animal," is inherent to the method. The isolation of antibodies from the an animal immunized by step a) of claim 6 for screening by step c) of claim 6 is inherent in the disclosure at, for example, page 42, lines 5-20, which describes the production of polyclonal antibodies. One of ordinary skill in the art would understand that one would necessarily have to isolate antibodies from an animal immunized according to step a) of claim 6 in order to carry out step c) of claim 6. Therefore, a skilled artisan would reasonably conclude that the inventors were in possession of all of the steps of the recited method, at the time the application was filed. For at least these reasons, the disclosure of U.S. applications 09/206,499 and 08/828,242 contains an adequate written description of the claimed subject matter, and claim 6 (and dependent claim 7) are entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997).

In regards to claims 8 and 9, the specification states that "[m]onoclonal antibodies to HCBP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EVB-hybridoma technique (Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; Cole S.P. et al. (1984) Mol. Cell Biol. 62:109-120)" (Specification at page 23, lines 25-28). These references were published over 10 years prior to the filing date of U.S. application 08/828,242, indicating that the method recited in claim 8 is conventional to the art. Therefore, one of ordinary skill in the art would understand that the inventors were in possession of the method recited by claim 8, including all of the individually recited method steps, at the time that U.S. application 08/828,242 was filed (March 31, 1997). For at least these reasons, the disclosure of the specification contains an adequate written description of the claimed subject matter, and claim 8 (and dependent claim 9) are entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997).

Furthermore, the references cited in the previous paragraph were explicitly incorporated by reference into the specification (e.g., at page 43, lines 10-11). Therefore, the steps of the method recited by claim 8 are supported by these references. For example, the Kohler reference (cited by the Office Action of July 24, 2003 at, e.g., page 23) is explicitly cited in the specification at page 23, line 28, and therefore is incorporated by reference into the application. The Kohler reference refers to cell lines which were "made by fusion of a mouse myeloma and mouse spleen cells from an immunised donor" (e.g., on page 495, 1st column, 1st paragraph), providing support for steps a)-c) of the method recited by claim 8. In addition, the Kohler reference discloses the growth of hybridoma cells in culture (e.g., on page 495, 2nd column, lines 2-5 from the top), supporting step d) of the method recited by claim 8. Furthermore, the Kohler reference provides an example of isolated monoclonal antibodies (e.g., in Figure 3 on page 497), providing support for step e) of the method recited by claim 8. For at least these reasons, the disclosure of the specification contains an adequate written description of the claimed subject matter, and claim 8 (and dependent claim 9) are entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997).

With respect to claim 21, the Office Action asserts that "the application, as originally filed, does not appear to describe a composition comprising an antibody and further comprising a label, but only such a composition where the antibody is joined to the label" (Office Action, July 24, 2003; page 6). However, compositions comprising an antibody and further comprising a label **are** adequately supported by the disclosure of the parent applications, U.S. application 09/206,499 and U.S. application 08/828,242.

Nevertheless, to expedite prosecution, claim 21 has been amended such that the recited composition comprises an antibody, "wherein the antibody is joined, either covalently or non-covalently, with a label." Support for this amendment can be found in the specification at, for example, page 30, lines 20-22. By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include compositions comprising an antibody and "further comprising a label." Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claim 21, as amended, recites patentable subject matter. The disclosure of U.S. applications 09/206,499 and 08/828,242 contains an adequate written description of the claimed subject matter, and claim 21, as amended, is entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997).

With respect to claims 22 and 23, the Office Action asserts that "[a]s originally filed, US Application No. 09/206,499 describes 'a suitable pharmaceutical carrier', but does not disclose 'a suitable carrier', *per se*; and the disclosure of suitable pharmaceutical carriers is not deemed sufficient to describe the broader genus of suitable carriers" (Office Action, July 24, 2003; page 6). However, compositions comprising an antibody and a suitable carrier **are** adequately supported by the disclosure of the parent applications, U.S. application 09/206,499 and U.S. application 08/828,242.

Nevertheless, to expedite prosecution, claims 22 and 23 have been amended such that the recited compositions comprise an antibody "and an excipient." Support for these amendments can be found in the specification at, for example, page 27, line 26 to page 28, line 1. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include compositions comprising an antibody and "a suitable carrier." Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claims 22 and 23, as amended, recite patentable subject matter. The disclosure of U.S. applications 09/206,499 and 08/828,242 contains an adequate written description of the claimed subject matter, and claims 22 and 23, as amended, are entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997).

III. Compliance with Sequence Rules

As requested by the Examiner, Applicants have submitted a Substitute Sequence Listing in order to comply with the Sequence Rules, and have amended the specification to identify each

disclosure of the sequences included in the Substitute Sequence Listing. For the Examiner's convenience, Applicants include herewith a copy of the Notice to Comply, a copy of the Response to Notice to Comply (mailed August 19, 2003), a copy of the Substitute Sequence Listing (mailed August 19, 2003), and a copy of the statement accompanying the Substitute Sequence Listing (mailed August 19, 2003).

IV. Objections to the specification

The specification was objected to based on the allegation that "the use of numerous improperly demarcated trademarks has been noted in this application" (Office Action, July 24, 2003; page 7, § 8).

As requested by the Examiner, the specification has been amended to properly demarcate trademarks using capitalization and accompanying generic terminology. Therefore, withdrawal of this objection is requested.

Applicants thank the Examiner for pointing out specific examples of improperly demarcated trademarks in the application.

The specification was objected to based on inadvertent and unintentional typographical errors and misspellings (Office Action, July 24, 2003; page 8, § 9).

In the present amendment, the inadvertent and unintentional typographical errors and misspellings indicated by the Examiner have been corrected. Therefore, withdrawal of this objection is requested.

Applicants thank the Examiner for pointing out the inadvertent typographical errors and misspellings.

V. Objections to the claims

Claim 5 was objected to based on the allegation that it is improperly dependent from claim 2 because the property "antagonist of a polypeptide comprising the amino acid sequence of SEQ ID NO:1," as recited by claim 5, would be inherent to the antibodies of claim 2 (Office Action, July 24, 2003; page 8, § 10). This objection is traversed.

The term "antagonist" is defined in the specification at page 5, lines 14-17, to "refer to a molecule which, when bound to HCBP, blocks or modulates the biological or immunological activity of HCBP." The blockage or modulation of the biological and/or immunological activity of HCBP is not inherent to all of the antibodies recited by claim 2. For example, an antibody which specifically binds to the SEQ ID NO:1 polypeptide may not block the calcium binding activity of the polypeptide if the binding between the antibody and the polypeptide occurs outside of the calcium-binding sites of the polypeptide.

Since "antagonist of a polypeptide comprising the amino acid sequence of SEQ ID NO:1" is not an inherent property of all of the antibodies of claim 2, claim 5 further limits the subject matter of claim 2, from which claim 5 depends.

For at least these reasons, withdrawal of this objection is requested.

VI. Utility rejection under 35 U.S.C. § 101

The rejection of claims 2-12 and 21-26 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

In this rejection, the Office Action focuses on the alleged lack of utility of the polypeptides which are specifically bound by the claimed antibodies. Based on this alleged lack of utility of the polypeptides, the Office Action asserts that the only use for the claimed antibodies is to carry out further research on the polypeptides specifically bound by the antibodies. However, the Office Action is incorrect in asserting that the claimed antibodies would lack utility without first "performing additional experimentation to characterize the functional significance of the polypeptide of SEQ ID NO:1, or the polynucleotide sequence encoding SEQ ID NO:1 in the pathology or etiology of a disease, or in the pharmacology of a particular drug" (Office Action, July 24, 2003; page 12). The claimed antibodies have specific, substantial, and credible utilities in, for example, the purification and/or detection of polypeptides. It is the polypeptides which are the object of further research, not the claimed antibodies. In these methods, the claimed antibodies are tools which facilitate research on the

polypeptides. For example, purification of polypeptides using the claimed antibodies has the useful benefit of providing the polypeptides in a form suitable for further research on the polypeptides. In another example, detection of polypeptides using the claimed antibodies has the useful benefit of monitoring the presence and/or amount of the polypeptides during research on the polypeptides. In such methods, the claimed antibodies are a research tool, and therefore have specific, substantial, and credible utilities.

Much of the Office Action's argument focuses on the alleged lack of utility of the polypeptides which are specifically bound by the claimed antibodies. For example, the Office Action asserts that:

> "until the further characterization of the protein encoded by the newly discovered polynucleotide sequence has been completed establishing the protein's putative function, the polynucleotide sequence is only a novelty, and the claimed antibody is therefore not a finished invention having an established utility." (Office Action, July 24, 2003; page 9)

and that:

> "there are dissimilarities between the amino acid sequence set forth in SEQ ID NO:1 and the amino acid sequence of other proteins, including reticulocalbin. The skilled artisan cannot reliably or accurately predict the effects of amino acid sequence dissimilarities." (Office Action, July 24, 2003; page 13)

However, the claims at issue are drawn to **antibodies**. The claimed antibodies have specific, substantial, and credible utilities in, for example, the purification and/or detection of polypeptides. It is improper for the Patent Office to base the instant rejection on the alleged lack of utility of the recited polypeptides because the claims are drawn to the recited antibodies, not to the recited polypeptides. Nevertheless, in the interest of providing a complete response to the Office Action's arguments, Applicants address the utility of the claimed antibodies based on the specific, substantial, and credible utilities of the recited polypeptides, below.

Furthermore, the Office Action asserts that the claimed invention could not be used in diagnostic or therapeutic applications due to unpredictability of the art, citing Ward (Develop. Oncol., 1985, 21:90-106), Tockman et al. (Cancer Res., 1992, 52:2711s-2718s), Gura (Science, 1997, 278:1041-1042), and Bergers et al. (Curr. Opin. Genet. Develop., 2000, 10:120-127). The Office Action states that "given only the benefit of Applicants' present disclosure, the skilled artisan could not

use the claimed invention [as a diagnostic marker] without having to perform additional experimentation of such complexity and measure that the public would not have derived any specific and substantial benefit" (Office Action, July 24, 2003; page 15), and that "because the disclosure is devoid of data generated by such empirical determinations, the skilled artisan would have to perform complex and lengthy courses of experimentation before the claimed invention might be used" as a therapeutic (Office Action, July 24, 2003; page 16). These assertions ignore the specific and substantial utility of the claimed invention in toxicology testing for drug discovery, discussed below.

The invention at issue, identified in the patent application as an antibody to HCBP, is an antibody to a polypeptide encoded by a gene that is expressed in immortalized, cancerous, fetal, and proliferative tissues of humans (Specification, e.g., at page 10, lines 1-3 and 20-23; page 11, lines 5-8; and page 21, lines 29-30). The novel polypeptide HCBP is demonstrated in the specification to be a member of the calcium-binding protein family (e.g., at page 10, lines 8-20), whose biological functions include binding and regulating calcium (e.g., at page 1, lines 19-32). The claimed antibody has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide bound by the claimed antibody actually functions biologically. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

The fact that the polypeptide bound by the claimed antibody is a member of the calcium-binding protein family alone demonstrates utility. Each of the members of this class, regardless of their particular functions, are useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the polypeptide bound by the claimed antibody also has patentable utility, regardless of its actual function. The law has never required a patentee to prove more. Analogously, the claimed antibody also has patentable utility, as it can be used, *inter alia*, to purify and detect the polypeptide to which it specifically binds.

There is, in addition, direct proof of the utility of the claimed invention. Applicants submit with this response the declaration of Lars Michael Furness describing some of the practical uses of the

claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of filing of the patent application. The Furness Declaration describes, in particular, how the polypeptide bound by the claimed antibody can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate (Furness Declaration at ¶ 10).

The Office Action does not dispute that the polypeptide bound by the claimed antibody can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Office Action contends that the polypeptide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed antibody in the absence of any knowledge as to the precise function of the protein bound by the claimed antibody. The uses of the polypeptide bound by the claimed antibody for gene and protein expression monitoring applications including toxicology testing are in fact independent of its precise biological functions.

The Office Action states that "the asserted utilities of the claimed invention that are disclosed in the specification are founded upon a presumption that the protein to which the antibody must bind will have activity similar to reticulocalbin, or will be associated with the etiology of a disorder of cellular proliferation, such as cancer or an hyperproliferative immune disorder" (Office Action, July 24, 2003; page 12). However, an association between the polypeptides bound by the claimed antibodies, and the etiology of a disorder of cellular proliferation, is not necessary in order for the claimed antibodies to have specific and substantial utility. For example, the claimed antibodies have utility in purifying and/or detecting the SEQ ID NO:1 polypeptide, which is itself useful in toxicology testing for drug discovery. The basis of this specific and substantial utility for the claimed antibodies is the expression of HCBP in human tissue.

While it is true that all polypeptides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for

utility does not preclude that utility from being specific, substantial, and credible. A toxicology test using any particular expressed polypeptide is dependent on the **identity** of that polypeptide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polypeptide in toxicology testing is specific to both the compound being tested and the polypeptide used in the test. No two human-expressed polypeptides are interchangeable for toxicology testing because the effects on the expression of any two such polypeptides will differ depending on the identity of the compound tested and the **identities** of the two polypeptides. It is not necessary to know the biological functions and disease associations of the polypeptides in order to carry out such toxicology tests. Therefore, it is not necessary to show that the polypeptides bound by the claimed antibodies are "associated with the etiology of a disorder of cellular proliferation" in order for the claimed antibodies to have a specific and substantial utility in toxicology testing. At the very least, the polypeptides bound by the claimed antibodies are specific controls for toxicology tests in developing drugs targeted to other polypeptides, and are clearly useful as such.

Furthermore, because any expressed polypeptide can be used as a specific control in a toxicology test for developing drugs targeted to other polypeptides, the claimed antibodies which specifically bind to the recited polypeptide variants of SEQ ID NO:1 have utilities that meet the requirements of 35 U.S.C. § 101. The recited polypeptide variants of SEQ ID NO:1 have naturally occurring amino acid sequences. It is useful to know if the expression of any such polypeptide is altered in response to exposure to an exogenous compound such as a drug candidate targeted to another polypeptide. This is true even if one does not know the biological functions or disease associations of a polypeptide used in such a toxicology test. Therefore, the recited polypeptide variants of SEQ ID NO:1, and antibodies which specifically bind to them, have utilities that meet the requirements of 35 U.S.C. § 101. Insofar as the arguments below apply to the specific and substantial utilities of antibodies to the SEQ ID NO:1 polypeptide which are due to the expression of the SEQ ID NO:1 polypeptide in naturally occurring tissues, these same arguments also apply to antibodies to polypeptide variants of SEQ ID NO:1 having naturally occurring amino acid sequences.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examining Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Purification and detection of a polypeptide which is useful in protein expression applications, including the techniques of two-dimensional polyacrylamide gel electrophoresis and western blot analysis, for drug development and toxicity testing, are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Furness Declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The membership of the polypeptide bound by the claimed antibody in the calcium-binding protein family demonstrates utility

Because there is a substantial likelihood that the HCBP polypeptide, which is bound by the claimed antibody, is a member of the family of polypeptides known as calcium-binding proteins, the members of which are indisputably useful, there is by implication a substantial likelihood that the polypeptide bound by the claimed antibody is similarly useful. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the polypeptide bound by the claimed antibody is a protein having the sequence shown as SEQ ID NO:1 in the patent application and referred to as HCBP in that application. Applicants have demonstrated by more than reasonable probability that HCBP is a member of the calcium-binding protein family. For example, HCBP shares "chemical and structural homology with a human reticulocalbin (GI 1262329; SEQ ID NO:3) and a mouse reticulocalbin (GI 220582; SEQ ID NO:4). In particular, HCBP shares 51% and 54% identity with the human and the mouse reticulocalbin, respectively" (Specification, e.g., at page 10, lines 16-19; and Figures 2A and 2B). Also, "HCBP and the human reticulocalbin have rather similar hydrophobicity plots" (e.g., at page 10, lines 19-20; and Figures 3A and 3B). Furthermore, HCBP "has six calcium-binding EF-hand motifs encompassing residues A90-L102, D126-L138, [D176-L188], D213-Y225, D254-V266, and D290-I302, and the conserved ER lumen retention signal HDEL (SEQ ID NO:6)" (e.g., at page 10, lines 10-12). The possession of six calcium-binding EF-hand motifs and a conserved ER lumen retention signal is a characteristic of reticulocalbin (e.g., at page 1, lines 28-32). In combination, these facts provide more than enough evidence to demonstrate a reasonable probability that the utility of calcium-binding proteins can be imputed to the polypeptides bound by the claimed antibodies.

The Patent Office must accept the Applicant's demonstration that the polypeptide bound by the claimed antibody is a member of the calcium-binding protein family and that utility is proven by a reasonable probability unless it can be demonstrated through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Office has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Patent Office provided any evidence that any member of the calcium-binding protein family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the polypeptide bound by the claimed antibody must, like the other members of the calcium-binding protein family, be useful.

The Office Action asserts that, while calcium-binding proteins are generically useful, "[a]ny calcium-binding agent can be used to chelate calcium; and anyway, EGTA, for example could more aptly be used as a chelating, or calcium-binding agent" (Office Action, July 24, 2003; page 11). The Office Action doesn't point to any law, however, that says a utility that is shared by a large class is somehow not a utility. If all of the class of calcium-binding proteins can be so used, then they all have utility. The issue is whether the claimed invention has any utility, not whether other compounds have a similar utility. Nothing in the law says that an invention must have a "unique" utility. Indeed, the whole notion of "well established" utilities **presupposes** that many different inventions can have the exact same utility. If the Office Action's argument was correct, there could never be a well established utility, because you could always find a generic group with the same utility! Furthermore, it is irrelevant whether EGTA would be a better calcium-binding agent than any particular calcium-binding protein. As long as a calcium-binding protein can act as a calcium-binding agent, it has utility. There is no requirement that the utility of an invention be the best possible way of carrying out that utility.

While the Patent Office has cited literature identifying some of the difficulties that may be involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in this case. Bowie et al., Science, 1990, 247:1306-1310; Burgess et al., J. Cell Biol., 1990, 111:2129-2138; Lazar et al., Mol. Cell. Biol., 1998, 8:1247-1252; Skolnick et al., Trends Biotechnol., 2000, 18:34-39. Importantly, none contradicts Brenner's basic rule that sequence homology in excess of 30% over at least 150 amino acid residues, or 40% over 70 or more amino acid residues, yields a high probability of functional homology as well. Brenner et al., Proceedings of the National Academy of Sciences USA, 1998, 95:6073-6078. In addition, none contradicts the findings of Bork that there is a 70% accuracy rate for bioinformatics-based predictions in general, and a 90% accuracy rate for the prediction of functional features by homology. Bork, Genome Res., 2000, 10:398-400. Furthermore, nor do these articles contradict the fact that the identification of the

polypeptide bound by the claimed antibody using a combination of independent methods provides compelling scientific evidence that the polypeptide has the biological functions of a calcium-binding protein. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

B. The uses of the polypeptides bound by the claimed antibodies for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene and protein expression profiling. These uses are explained in detail in the accompanying Furness Declaration, the substance of which is not rebutted by the Patent Office. There is no dispute that the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

The instant application is a divisional of, and claims priority to, Hillman et al. (U.S. Ser. No. 09/206,499, filed December 7, 1998; hereinafter "the Hillman '499 application"), which is a divisional of, and claims priority to, Hillman et al. (U.S. Ser. No. 08/828,242, filed March 31, 1997; hereinafter "the Hillman '242 application"). The instant application, and the Hillman '499 and Hillman '242 applications, were filed with essentially identical specifications, with the exception of corrected typographical errors and reformatting. Thus page and line numbers may not match as between the instant application, and the Hillman '499 and Hillman '242 applications.

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the application at issue (U.S. Ser. No. 09/768,840) on March 31, 1997 (the filing date of the Hillman '242 application) would have understood that application to disclose the polypeptides bound by the claimed antibodies to be useful for a number of gene and protein expression monitoring applications, e.g., in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs (Furness Declaration at, e.g., ¶¶ 10-13). Much, but not all, of

Mr. Furness' explanation concerns the use of the polypeptides bound by the claimed antibodies in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, e.g., in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. Furness Declaration at ¶ 10.

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states of tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Hillman '242 application . . . and other related pre-March 1997 publications, persons skilled in the art on March 31, 1997 clearly would have understood the Hillman '242 application to disclose the SEQ ID NO:1 polypeptide, and the antibody to a SEQ ID NO:1 polypeptide, to be useful in 2-D PAGE analyses for the development of new drugs and for monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity . . . (Furness Declaration, page 8, ¶ 10)

> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:1 polypeptide would be a more useful tool than a 2-D PAGE map that did not utilize this polypeptide in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating disorders associated with cell proliferation for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, page 10, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before March 1997. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference

gel images, constructed from one or more gels, form the basis of two-dimensional gel databases. (Wilkins at page 26, Furness Declaration at Tab C).

C. The use of polypeptides expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Mr. Furness in his declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, e.g., John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: Practicalities, problems, and potential, Xenobiotica, 1999, 29:655-691:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett et al., page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis, 1999, 24:153-159; Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters, 2000, 112-113:467-471.

The more genes -- and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir article, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Evidence of the benefits of this information include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Office failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the rejections should be withdrawn regardless of their merit.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequences of polypeptides bound by the claimed antibodies and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's invention of the polypeptide bound by the claimed antibody, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase polynucleotides encoding the polypeptide bound by the claimed antibody directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described *supra*.

III. The Office Action's rejections are without merit

Rather than responding to the evidence demonstrating utility, the Office Action attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the polypeptide bound by the claimed antibody are not "specific and substantial asserted" utilities (Office Action, July 24, 2003; page 9). The Office Action is incorrect both as a matter of law and as a matter of fact.

A. The precise biological role or function of an expressed polypeptide is not required to demonstrate utility

The Office Action's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the polypeptide bound by the claimed

antibody, the claimed invention's utility is not sufficiently specific. According to the Office Action, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the polypeptide bound by the claimed antibody either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Office Action would require, in addition, that the Applicants provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Office Action would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, e.g., ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any polypeptide or antibody invention, the Office Action has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the polypeptide bound by the claimed antibody, the Patent Office should have looked first to the benefits the claimed invention is alleged to provide.

B. Membership in a class of useful products can be proof of utility

Despite the evidence that the polypeptide bound by the claimed antibody is a member of the calcium-binding protein family, whose members indisputably are useful, the Office Action refused to impute the utility of the members of this class to HCBP. The Office Action of July 24, 2003 takes the position that unless Applicants can identify which particular biological functions within the class of calcium-binding proteins is possessed by HCBP, utility cannot be imputed. To demonstrate utility by membership in the class of calcium-binding proteins, the Office would require that all calcium-binding proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately

useless members. See, *e.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[1]

The Office Action addresses HCBP as if the general class in which it is included is not the calcium-binding protein family, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the calcium-binding protein family does not. The calcium-binding protein family is sufficiently specific to rule out any reasonable possibility that HCBP would not also be useful like the other members of the family.

Because the Office Action has not presented any evidence that the class of calcium-binding proteins has any, let alone a substantial number, of useless members, the Office Action must conclude that there is a "substantial likelihood" that HCBP is useful. It follows that the claimed antibody to HCBP also is useful.

Even if the Office Action's "common utility" criterion were correct – and it is not – the calcium-binding protein family would meet it. It is undisputed that known members of the calcium-binding protein family are proteins involved in binding and regulating calcium within cells. A person of ordinary skill in the art need not know any more about how the polypeptide bound by the claimed antibody participates in the regulation of calcium within cells to use it, and the Office Action presents no evidence to the contrary. Instead, the Office Action makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given calcium-binding protein regulates calcium in any particular cells. The Office Action then goes on to assume that the only use for antibodies which bind HCBP absent knowledge as to how this member of the class of calcium-binding proteins actually works is further study of HCBP itself.

Not so. As demonstrated by Applicants, knowledge that HCBP is a calcium-binding protein is more than sufficient to make the claimed antibodies useful for drug discovery and toxicology studies

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[1]At a Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

using protein expression anaylsis. Also, HCBP has been shown to be expressed in immortalized, cancerous, fetal, and proliferative tissues of humans, indicating utility in the diagnosis and treatment of disorders associated with cell proliferation. The Patent Office must accept these facts to be true unless the Office can provide evidence or sound scientific reasoning to the contrary. But the Patent Office has not done so.

C. The uses of polypeptides in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The Office Action rejected the claims at issue on the ground that the use of an invention as a tool for research is not a "substantial" use. Because the Office Action's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be withdrawn.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (M.P.E.P. § 2107.01):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the Patent Office's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely

because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the polypeptide bound by the claimed antibody have been demonstrated, in particular those described in the Furness Declaration. The Furness Declaration demonstrates that the claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide bound by the claimed antibody.

The Office Action asserts that "because an antibody is generically useful as a such a reagent, the assertion that the claimed antibody can be used as such lacks specificity" (Office Action, July 24, 2003; page 11). Not so. The use of the claimed invention as a research tool in toxicology testing is specific and substantial. While it is true that all antibodies which specifically bind to a polypeptide expressed in humans have utility in toxicology testing based on the expression of the polypeptide at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. A toxicology test using any particular expressed polypeptide is dependent on the **identity** of that polypeptide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polypeptide in toxicology testing is specific to both the compound being tested and the polypeptide used in the test. **No two human-expressed polypeptides are interchangeable for toxicology testing** because the effects on the expression of any two such polypeptides will differ depending on the identity of the compound tested and the **identities** of the two polypeptides. It is not necessary to know the biological functions and disease associations of the polypeptides in order to carry out such toxicology tests. Therefore, at the very least, the polypeptide bound by the claimed antibody is a specific control for toxicology tests in developing drugs targeted to other polypeptides, and the claimed antibody is useful for detecting and/or purifying the polypeptide.

As an example, a histone protein expressed in humans can be used in a specific and substantial toxicology test in drug development. A histone protein may not be suitable as a target for drug development because disruption of such a protein may kill a patient. However, a human-expressed histone protein is surely an excellent subject for toxicology studies when developing drugs **targeted to other proteins**. A drug candidate which alters expression of a histone protein is toxic because disruption of such a pervasively-expressed protein would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another protein, measuring the expression of a histone protein is a good measure of the toxicity of that candidate, particularly in *in vitro* cellular assays at an early stage of drug development. The utility of any particular human-expressed histone protein in toxicology testing is specific and substantial because a toxicology test using that histone protein cannot be replaced by a toxicology test using a different protein, including any other histone protein. This specific and substantial utility requires no knowledge of the biological function or disease association of the histone protein. This utility of the histone protein forms the basis of at least one of the specific and substantial utilities of an antibody which specifically binds to the histone protein.

The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include detection of an HCBP polypeptide (Specification, e.g., at page 20, lines 7-15), competitive drug screening assays (e.g., at page 35, lines 3-6), and purification of an HCBP polypeptide (e.g,. at page 42, lines 22-32), etc.

D. The Office Action failed to demonstrate that a person of ordinary skill in the art would reasonably doubt the utility of the claimed invention

Based principally on citations to scientific literature identifying some of the difficulties involved in predicting protein function, the Office Action rejected the pending claims on the ground that the Applicants cannot impute utility to the claimed invention based on the homology of the polypeptide bound by the claimed antibody to other polypeptides undisputed by the Office Action to be useful. The Office Action's rejection is both incorrect as a matter of fact and as a matter of procedural law.

As demonstrated in § II.A, *supra*, the literature cited by the Office Action is not inconsistent with the Applicants' proof of homology by a reasonable probability. It may show that Applicants cannot prove function by homology with **certainty**, but Applicants need not meet such a rigorous

standard of proof. Under the applicable law, once the Applicants demonstrate a *prima facie* case of homology, the Patent Office must accept the assertion of utility to be true unless the Patent Office comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. See *In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Patent Office has not made such a showing and, as such, the Office Action's rejection should be withdrawn.

In the present case, the Office Action contended that the degree of amino acid identity among HCBP and other calcium-binding proteins is insufficient to establish that HCBP is a member of the calcium-binding protein family and thus shares the same utilities. The Office Action attempted to support this assertion with the teachings of Bowie et al. (Science, 1990, 247:1306-1310), Burgess et al. (J. Cell Biol., 1990, 111:2129-2138), Lazar et al. (Mol. Cell. Biol., 1988, 8:1247-1252), and Skolnick et al. (Trends Biotechnol., 2000, 18:34-39), all of record and addressed below. However, all of these references fail to support the outstanding rejections.

Applicants submit that the teachings of Bowie et al. are, in part, counter to the outstanding rejections, and in part, supportive of the asserted utilities of HCBP based on amino acid sequence homology to calcium-binding proteins. Careful review of this reference reveals that the teachings of Bowie et al. are directed primarily toward studying the effects of site-directed substitution of amino acid residues in certain proteins in order to determine the relative importance of these residues to protein structure and function. As discussed below in further detail, such experiments are not relevant to Applicants' use of amino acid sequence homology to reasonably predict protein function.

In support of Applicants' use of amino acid sequence homology to reasonably predict the utility of the polypeptide bound by the claimed antibody, Bowie et al. teach that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues that have been conserved over the course of evolution (Bowie et al., page 1306, 1st column, last paragraph, and 2nd column, 2nd full paragraph; page 1308, 1st column, last paragraph; page 1310, 1st column, last paragraph). It is known in the art that natural selection acts to conserve protein function. As taught by Bowie et al., proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to

occur. Conversely, mutations that reduce or abolish protein function are eliminated by natural selection. Based on these central tenets of molecular evolution, Applicants submit that the amino acid differences among the polypeptide bound by Applicants' claimed antibody and known calcium-binding proteins are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would further conclude that the level of conservation observed between the polypeptide bound by Applicants' claimed antibody and calcium-binding proteins is indicative of a common function, and hence, common utility, among these proteins.

In further support of Applicants' use of amino acid sequence homology to reasonably predict the biological function of the polypeptide bound by the claimed antibody, Applicants provide the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA, 1998, 95:6073-6078). Through exhaustive analysis of a dataset of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., page 6076). As shown in Figures 2A and 2B and as reported in the specification, SEQ ID NO:1 shares 51% identity with human reticulocalbin (GenBank ID 1262329; SEQ ID NO:3), and 54% identity with mouse reticulocalbin (GenBank ID 220582; SEQ ID NO:4) over about 328 amino acids (e.g., at page 10, lines 16-19), thus meeting the criteria of Brenner et al. Therefore, SEQ ID NO:1 and the human and mouse reticulocalbins share sequence identity that exceeds the thresholds proposed by Brenner et al., and SEQ ID NO:1 is a true reticulocalbin homolog by these criteria. Since these criteria are based on a dataset of homologous proteins with shared structural and functional features, one of ordinary skill in the art would likewise expect SEQ ID NO:1 to possess the evolutionarily conserved structural and functional characteristics of reticulocalbins. Hence, the "reasonable correlation" standard as set by case law has been met.

The use of such sequence comparisons to predict protein function is supported by Bork (Genome Res., 2000, 10:398-400). Bork discloses a 70% accuracy rate in bioinformatics-based predictions. This more than meets the legal standard of utility, which requires only that one of skill in the

art would **more likely than not** believe the utility of the claimed invention. For predicting functional features by homology, Table 1 of Bork discloses a 90% accuracy rate, even greater than the 70% accuracy rate for all bioinformatics predictions.

The Office Action further cited Burgess et al. and Lazar et al. as demonstrating that even a single amino acid change can alter protein function. However, these references are not relevant to the case at hand. Burgess et al. describe mutagenesis of HBGF-1 at an amino acid residue known to be important for ligand binding. Similarly, Lazar et al. describe the mutagenesis of two amino acid residues that are highly conserved among EGFs and TGF-αs. In both of these cases, particular amino acid residues with known importance to protein function were specifically targeted for site-directed mutagenesis. These mutations were "artificially" created in the laboratory and, therefore, are **not** analogous to molecular evolution, which is profoundly influenced by natural selection. For example, the deactivating mutations as described by Burgess et al. and Lazar et al. would almost certainly not be tolerated in nature. Furthermore, it is clear that over the course of evolution, amino acid residues that are critical for protein function are **conserved**. Thus, the amino acid differences between SEQ ID NO:1 and the human and mouse reticulocalbins are likely to represent substitutions that do **not** alter protein function. Therefore, the teachings of Burgess et al. and Lazar et al. are not relevant to the case at hand.

One could then argue that partial loss-of-function mutations do occur in nature, for example, the mutation in hemoglobin that causes sickle cell anemia. However, this example is the **rare** exception in evolution, **not the rule**. Persistence of such a mutation in a population would **not** be expected by one of ordinary skill in the art. Persistence occurs only because of the fluke of heterozygous advantage. Therefore, the Office Action's assertion that one of skill in the art would routinely expect to find single amino acid substitutions that drastically affect the function of the individual members of a conserved protein family is entirely unsubstantiated. Furthermore, in those rare cases where a partial loss-of-function mutation is persistent, the fact remains that the mutant polypeptide **still retains the utility of the non-mutant polypeptide**. The utility of the mutant polypeptide is the same as that of the non-mutant polypeptide, even though the results achieved are not equivalent. **Some** utility, not **perfect** utility, is all that is statutorily required for patentable utility.

The Office Action cites Skolnick et al. as evidence that "the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*)" (Office Action, July 24, 2003; page 14; emphasis in original). The Skolnick reference proposes that, instead of sequence comparisons or structural comparisons by themselves, "[w]hat we really need to analyse and predict the multifunctional aspects of proteins is a method specifically to recognize active sites and binding regions" (Skolnick et al., page 35, first column, second paragraph). Thus, Skolnick et al. supports the use of motif searches in combination with sequence alignments to provide a more robust method of predicting protein function. Just such a method has been used in predicting the relationship between HCBP and calcium-binding proteins such as reticulocalbin, encompassing not just sequence comparison, but identification of specific functional motifs such as the six EF-hand calcium-binding motifs and a conserved ER lumen retention signal (Specification, e.g., at page 10, lines 10-12). The methods used to identify HCBP are, in effect, "what we really need." Furthermore, the Skolnick reference recognizes that assigning function based on sequence homology is a "powerful" method (Skolnick et al., page 34, right-hand column, third paragraph). As such, the Skolnick reference supports the notion that HCBP has the utilities and biological functions of calcium-binding proteins.

As the cited evidence is completely insufficient to support the rejections of the claims, the outstanding rejections must be withdrawn for this reason alone. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the polypeptide bound by the claimed antibody is in fact a member of the family of calcium-binding proteins, which are known to have specific utility.

There is, in addition, further evidence that the polypeptide bound by the claimed antibody has the biological functions of the calcium-binding protein family. For example, the prediction that HCBP is a calcium-binding protein similar to reticulocalbin is based on more than just sequence comparison. HCBP, and the human and mouse reticulocalbins, all have EF-hand calcium-binding motifs and a conserved ER lumen retention signal. The identification of these motifs and domains in HCBP, none of

which have been adequately considered by the Patent Office, provides independent confirmation of the results of sequence comparison.

A critical examination of the literature, in conjunction with the disclosure of the instant application, shows that a relationship between HCBP and reticulocalbin is justified, and that one of skill in the art would reasonably conclude that HCBP has the biological functions of calcium-binding proteins such as reticulocalbin based on objective criteria. Therefore, the subject application has adequately disclosed at least one utility of the claimed invention based on the biological function of HCBP as a calcium-binding protein. These utilities are in addition to the well established utilities of HCBP in toxicology testing and drug discovery, which are not dependent on the specific biological function of HCBP.

IV. By requiring the Patent Applicant to assert a particular or unique utility, the Patent Examination Utility Guidelines and Training Materials applied by the Patent Office misstate the law

There is an additional, independent reason to withdraw the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at page 52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra*, § III.B (*Montedison,* 664 F.2d at 374-375).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. See *supra* § III.B. Thus the Training Materials cannot be applied consistently with the law.

VII. Utility/enablement rejection under 35 U.S.C. § 112, first paragraph

Claims 2-12 and 21-26 were rejected under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility under 35 U.S.C. § 101.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under 35 U.S.C. § 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 U.S.C. § 101, it fails for the same reasons.

VIII. Written description rejection of "variants" under 35 U.S.C. § 112, first paragraph

Claims 2-12, 21-23, and 26 were rejected under 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. The Office Action states that "the skilled artisan could not envision, or even predict the structure of any other naturally occurring variants of the polypeptide of SEQ ID NO:1, which have the ability to bind calcium, even given only the benefit of the disclosure, as the structure of naturally occurring polypeptides can only be determined empirically" (Office Action, July 24, 2003; pages 17-18). This rejection is traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.* *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. [footnotes omitted]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the claimed antibodies which specifically bind to the recited "variants" of SEQ ID NO:1.

The subject matter encompassed by claims 2-12, 21-23, and 26 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 2 recites polypeptides "comprising a naturally occurring amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO:1." The amino acid sequence of SEQ ID NO:1 is explicitly disclosed in the specification. See, for example, the Sequence Listing and Figures 1A, 1B, 1C, 2A, and 2B. Variants of SEQ ID NO:1 are

described in the specification at, for example, page 4, lines 12-15 and 22-30; page 10, lines 24-27; and page 12, lines 11-18.

One of ordinary skill in the art would recognize polypeptide sequences which are variants that are at least 80% identical to SEQ ID NO:1. Given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1. Accordingly, the specification provides an adequate written description of the claimed antibodies which specifically bind to the recited polypeptide variants of SEQ ID NO:1.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For

example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define the polypeptides bound by the claimed antibodies in terms of chemical structure, rather than functional characteristics. For example, the language of independent claim 2 recites chemical structure to define the claimed genus:

> 2. An isolated antibody which specifically binds to a polypeptide selected from the group consisting of:
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide binds calcium,
> c) a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment binds calcium,
> . . .

f) a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment comprises residues D254-V266 of SEQ ID NO:1, and

. . .

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides specifically bound by the claimed antibodies. The polypeptides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base the written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

The Patent Office Guidelines indicate that evidence that Applicants were in possession of the claimed invention can include "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, **or** some combination of such characteristics" (P.T.O. Guidelines, *supra*; emphasis added). The claimed antibodies which specifically bind the recited variants of the SEQ ID NO:1 polypeptide have been described by chemical structure (e.g., relation of the recited polypeptide variants to SEQ ID NO:1), physical properties (e.g., occurrence in nature of the recited polypeptide variants), and chemical properties (e.g., specific binding to the recited polypeptide variants; calcium-binding activity of the recited polypeptide variants). Therefore, the written description requirement has been met.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that, rather than being a large variable genus, the genus of polypeptides recited by the claims is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA, 1998, 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to antibodies which specifically bind to polypeptides which are calcium-binding proteins including polypeptides which are calcium-binding proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as calcium-binding proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites a polypeptide "comprising a naturally occurring amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 328 amino acid residues). This variation is far less than that of all potential calcium-binding proteins related to SEQ ID NO:1, i.e., those calcium-binding proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1. It follows that the genus of claimed antibodies is far less variant than that of antibodies which specifically bind to all potential calcium-binding proteins related to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an

Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of March 31, 1997. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed antibodies which specifically bind the recited polypeptide variants at the time of filing of this application.

4. Summary

The Office Action failed to base the written description inquiry "on whatever is now claimed." Consequently, the Office Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims reciting nucleic acids and proteins. In addition, the genus of polypeptides recited by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed antibodies which specifically bind to the recited polypeptide "variants," and this rejection should be withdrawn.

IX. Written description/new matter rejection of claim 4 under 35 U.S.C. § 112, first paragraph

Claim 4 was rejected under 35 U.S.C. § 112, first paragraph, because the recitation of "an acceptable excipient" is allegedly new subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention. The Office Action asserts that "[t]he originally filed disclosure of US Application No. 09/206,499 does not include an adequate description of the broad genus of acceptable excipients to provide proper and sufficient antecedence. US Application No. 09/206,499 merely discloses, 'pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients' (column 20); and in this particular context, also discloses examples of 'suitable excipients' (column 20)" (Office Action, July 24, 2003; page 19, § 16). This rejection is traversed.

Compositions comprising an antibody and an acceptable excipient **are** adequately supported by the disclosure of the specification. Nevertheless, to expedite prosecution, claim 4 has been amended such that the recited compositions comprise an antibody "and an excipient." Support for this amendment can be found in the specification at, for example, page 27, line 26 to page 28, line 1. By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include compositions comprising an antibody and "an acceptable excipient." Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claim 4, as amended, recites patentable subject matter. Therefore, withdrawal of this rejection is requested.

X. Written description/new matter rejection of claims 6-9 under 35 U.S.C. § 112, first paragraph

Claims 6-9 were rejected under 35 U.S.C. § 112, first paragraph, because some of the steps of the methods recited by claims 6 and 8 are allegedly new subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention. The Office Action asserts that "[c]laims 6-9 recite method steps, which do not appear to be particularly described in the originally filed disclosure of US Application No. 09/206,499" (Office Action, July 24, 2003; pages 19-20). This rejection is traversed.

In determining whether there is adequate support in the specification to convey to a skilled artisan that the inventors had possession of the claimed invention, the M.P.E.P. provides that "[t]he subject matter of the claim need not be describe literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." M.P.E.P. § 2163.02. Thus, there is no requirement for the specification to literally recite each of the steps of the recited method claims. All that is required is that the specification **reasonably** conveys that the inventors were in possession of the claimed invention.

Furthermore, the M.P.E.P. provides that:

> To comply with the written description requirement of 35 U.S.C. 112, para. 1, or to be entitled to an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c), each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. When an explicit limitation in a claim 'is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation.' *Hyatt v. Boone*, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998). M.P.E.P. § 2163 at subsection II.3.(b)

Thus, there is no requirement that each step of the methods recited by claims 6 and 8 be literally described in the specification as long as a skilled artisan would reasonably understand that the inventors were in possession of the claimed invention.

Moreover:

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating 'the description need not be in *ipsis verbis* [i.e., 'in the same words'] to be sufficient'). M.P.E.P. § 2163 at subsection II.3.(a)

Therefore, an adequate written description does not require a detailed description of "[w]hat is conventional or well known" in the art. For example, since methods of preparing polyclonal and/or monoclonal antibodies are well known in the art, the explicit recitation of each of the steps of claim 6

and/or 8 is not required in order for the specification to provide an adequate written description of these claims. For at least these reasons, withdrawal of this rejection is requested.

In regards to claims 6 and 7, step a) of claim 6 is described in the specification at, for example, page 23, lines 10-24; and page 42, lines 16-17. Step c) of claim 6 is described in the specification at, for example, page 24, lines 20-26; and page 42, lines 17-20. Step b) of claim 6, which recites "isolating antibodies from the animal," is inherent to the method. The isolation of antibodies from the an animal immunized by step a) of claim 6 for screening by step c) of claim 6 is inherent in the disclosure at, for example, page 42, lines 5-20, which describes the production of polyclonal antibodies. One of ordinary skill in the art would understand that one would necessarily have to isolate antibodies from an animal immunized according to step a) of claim 6 in order to carry out step c) of claim 6. Therefore, a skilled artisan would reasonably conclude that the inventors were in possession of all of the steps of the recited method, at the time the application was filed. For at least these reasons, withdrawal of this rejection with respect to claims 6 and 7 is requested.

In regards to claims 8 and 9, the specification states that "[m]onoclonal antibodies to HCBP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EVB-hybridoma technique (Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; Cole S.P. et al. (1984) Mol. Cell Biol. 62:109-120)" (Specification at page 23, lines 25-28). These references were published over 10 years prior to the filing date of U.S. application 08/828,242 (the ultimate parent of the instant application), indicating that the method recited in claim 8 is conventional to the art. Therefore, one of ordinary skill in the art would understand that the inventors were in possession of the method recited by claim 8, including all of the individually recited method steps, at the time the application was filed. For at least these reasons, withdrawal of this rejection with respect to claims 8 and 9 is requested.

Furthermore, the references cited in the previous paragraph were explicitly incorporated by reference into the specification (e.g., at page 43, lines 10-11). Therefore, the steps of the method recited by claim 8 are supported by these references. For example, the Kohler reference (cited by the

Office Action of July 24, 2003 at, e.g., page 23) is explicitly cited in the specification at page 23, line 28, and therefore is incorporated by reference into the application. The Kohler reference refers to cell lines which were "made by fusion of a mouse myeloma and mouse spleen cells from an immunised donor" (e.g., on page 495, 1st column, 1st paragraph), providing support for steps a)-c) of the method recited by claim 8. In addition, the Kohler reference discloses the growth of hybridoma cells in culture (e.g., on page 495, 2nd column, lines 2-5 from the top), supporting step d) of the method recited by claim 8. Furthermore, the Kohler reference provides an example of isolated monoclonal antibodies (e.g., in Figure 3 on page 497), providing support for step e) of the method recited by claim 8. Therefore, one of ordinary skill in the art would understand that the inventors were in possession of the method recited by claim 8, including all of the individually recited method steps, at the time the application was filed. For at least these reasons, withdrawal of this rejection with respect to claims 8 and 9 is requested.

XI. Written description/new matter rejection of claim 21 under 35 U.S.C. § 112, first paragraph

Claim 21 was rejected under 35 U.S.C. § 112, first paragraph, because the recitation of "further comprising a label" is allegedly new subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention. The Office Action asserts that "the application, as originally filed, does not appear to describe a composition comprising an antibody and further comprising a label, but only such a composition where the antibody is joined to the label" (Office Action, July 24, 2003; page 20). This rejection is traversed.

Compositions comprising an antibody and further comprising a label **are** adequately supported by the disclosure of the specification. Nevertheless, to expedite prosecution, claim 21 has been amended such that the recited composition comprises an antibody, "wherein the antibody is joined, either covalently or non-covalently, with a label." Support for this amendment can be found in the specification at, for example, page 30, lines 20-22. By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include compositions comprising an antibody and

"further comprising a label." Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claim 21, as amended, recites patentable subject matter. Therefore, withdrawal of this rejection is requested.

XII. Written description/new matter rejection of claims 22 and 23 under 35 U.S.C. § 112, first paragraph

Claims 22 and 23 were rejected under 35 U.S.C. § 112, first paragraph, because the recitation of "a suitable carrier" is allegedly new subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention. The Office Action asserts that "[a]s originally filed, US Application No. 09/206,499 describes 'a suitable pharmaceutical carrier', but does not disclose 'a suitable carrier', *per se*; and the disclosure of suitable pharmaceutical carriers is not deemed sufficient to describe the broader genus of suitable carriers" (Office Action, July 24, 2003; page 20). This rejection is traversed.

Compositions comprising an antibody and a suitable carrier **are** adequately supported by the disclosure of the specification. Nevertheless, to expedite prosecution, claims 22 and 23 have been amended such that the recited compositions comprise an antibody "and an excipient." Support for these amendments can be found in the specification at, for example, page 27, line 26 to page 28, line 1. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include compositions comprising an antibody and "a suitable carrier." Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claims 22 and 23, as amended, recite patentable subject matter. Therefore, withdrawal of this rejection is requested.

XIII. Rejections under 35 U.S.C. § 112, second paragraph

Claims 4, 22, and 23 were rejected under 35 U.S.C. § 112, second paragraph, based on the allegation that the recitation of "acceptable excipient" and "suitable carrier" is indefinite. The Office Action asserts that "whether or not a particular excipient, or carrier is regarded by Applicants as

'acceptable', or 'suitable' cannot be determined by the practitioner in the absence of an explicit definition of the genus of 'acceptable' excipients and an explicit definition of the genus of 'suitable' carriers" (Office Action, July 24, 2003; page 21, § 18). This rejection is traversed.

Under the second paragraph of 35 U.S.C. § 112, the standard for "definiteness" is that the claims define patentable subject matter with a **reasonable** degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also M.P.E.P. § 706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give "fair" notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other words, the basic purpose of 35 U.S.C. § 112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonius v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir.1983). Claims 4, 22, and 23 meet the legal standards required by 35 U.S.C. § 112, second paragraph.

Nevertheless, to expedite prosecution, claims 4, 22, and 23 have been amended such that the recited compositions comprise an antibody "and an excipient." Support for these amendments can be found in the specification at, for example, page 27, line 26 to page 28, line 1. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include compositions comprising an antibody and either "an acceptable excipient" or "a suitable carrier." Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claims 4, 22, and 23, as amended, recite patentable subject matter. One of skill in the art would reasonably understand the metes and bounds of claims 4, 22, and 23, as amended. For at least these reasons, reversal of this rejection under 35 U.S.C. § 112, second paragraph, is requested.

XIV. Rejection of claims 4, 7, 9, 22, and 23 under 35 U.S.C. § 102(b) by WO 98/44114 A1

Claims 4, 7, 9, 22, and 23 were rejected under 35 U.S.C. § 102(b) because the recited antibodies and compositions are allegedly anticipated by PCT publication WO 98/44114 A1. The Office Action asserts that PCT publication WO 98/44114 A1 "discloses compositions comprising monoclonal or polyclonal antibodies, which bind specifically to the polypeptide of SEQ ID NO:1, and an acceptable excipient or a suitable carrier" (Office Action, July 24, 2003; page 22, § 20). This rejection is traversed.

This rejection is based on the allegation that claims 4, 7, 9, 22, and 23 are not entitled to the benefit of the filing dates of U.S. applications 09/206,499 and 08/828,242. As discussed above under § II, claims 7 and 9, and amended claims 4, 22, and 23, are entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997). Therefore, PCT publication WO 98/44114 A1 does not anticipate the claimed subject matter.

For at least the above reasons, withdrawal of this rejection is requested.

XV. Rejection of claim 4, 7, 9, 22, and 23 under 35 U.S.C. § 102(b) by U.S. 5,976,801 A

Claims 4, 7, 9, 22, and 23 were rejected under 35 U.S.C. § 102(b) because the recited antibodies and compositions are allegedly anticipated by U.S. Patent No. 5,976,801 A. The Office Action asserts that U.S. Patent No. 5,976,801 A "discloses compositions comprising monoclonal or polyclonal antibodies, which bind specifically to the polypeptide of SEQ ID NO:1, and an acceptable excipient or a suitable carrier" (Office Action, July 24, 2003; page 22, § 21). This rejection is traversed.

This rejection is based on the allegation that claims 4, 7, 9, 22, and 23 are not entitled to the benefit of the filing dates of U.S. applications 09/206,499 and 08/828,242. As discussed above under § II, claims 7 and 9, and amended claims 4, 22, and 23, are entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997). Therefore, U.S. Patent No. 5,976,801 A does not anticipate the claimed subject matter.

For at least the above reasons, withdrawal of this rejection is requested.

XVI. Rejections under 35 U.S.C. § 102(e)

Claims 4, 7, 9, 22, and 23 were rejected under 35 U.S.C. § 102(e) because the recited antibodies and compositions are allegedly anticipated by U.S. Patent No. 6,235,477 B1. The Office Action asserts that U.S. Patent No. 6,235,477 B1 has an earlier effective U.S. filing date, and that it "discloses compositions comprising monoclonal or polyclonal antibodies, which bind specifically to the polypeptide of SEQ ID NO:1, and an acceptable excipient or a suitable carrier" (Office Action, July 24, 2003; page 23). This rejection is traversed.

This rejection is based on the allegation that claims 4, 7, 9, 22, and 23 are not entitled to the benefit of the filing dates of U.S. applications 09/206,499 and 08/828,242. As discussed above under § II, claims 7 and 9, and amended claims 4, 22, and 23, are entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997). Therefore, U.S. Patent No. 6,235,477 B1 does not anticipate the claimed subject matter.

For at least the above reasons, withdrawal of this rejection is requested.

XVII. Rejection of claims 4, 6-9, and 21-23 under 35 U.S.C. § 103(a) over WO 98/44114 in view of Kohler et al.

Claims 4, 6-9, and 21-23 were rejected under 35 U.S.C. § 103(a) because the claimed antibodies, compositions, and methods of making antibodies are allegedly obvious over PCT publication WO 98/44114 A1 in view of Kohler et al. (Nature, 1975, 256:495-497). This rejection is traversed.

This rejection is based on the allegation that claims 4, 6-9, and 21-23 are not entitled to the benefit of the filing dates of U.S. applications 09/206,499 and 08/828,242. As discussed above under § II, claims 6-9, and amended claims 4 and 21-23, are entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997). Therefore, the claimed subject matter is not obvious over PCT publication WO 98/44114 A1 in view of Kohler et al.

For at least the above reasons, withdrawal of this rejection is requested.

XVIII. Rejection of claims 4, 6-9, and 21-23 under 35 U.S.C. § 103(a) over U.S. 5,976,801 A in view of Kohler et al.

Claims 4, 6-9, and 21-23 were rejected under 35 U.S.C. § 103(a) because the claimed antibodies, compositions, and methods of making antibodies are allegedly obvious over U.S. Patent No. 5,976,801 A in view of Kohler et al. (Nature, 1975, 256:495-497). This rejection is traversed.

This rejection is based on the allegation that claims 4, 6-9, and 21-23 are not entitled to the benefit of the filing dates of U.S. applications 09/206,499 and 08/828,242. As discussed above under § II, claims 6-9, and amended claims 4 and 21-23, are entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997). Therefore, the claimed subject matter is not obvious over U.S. Patent No. 5,976,801 A in view of Kohler et al.

For at least the above reasons, withdrawal of this rejection is requested.

XIX. Rejection of claims 4, 6-9, and 21-23 under 35 U.S.C. § 103(a) over U.S. 6,235,477 B1 in view of Kohler et al.

Claims 4, 6-9, and 21-23 were rejected under 35 U.S.C. § 103(a) because the claimed antibodies, compositions, and methods of making antibodies are allegedly obvious over U.S. Patent No. 6,235,477 B1 in view of Kohler et al. (Nature, 1975, 256:495-497). This rejection is traversed.

This rejection is based on the allegation that claims 4, 6-9, and 21-23 are not entitled to the benefit of the filing dates of U.S. applications 09/206,499 and 08/828,242. As discussed above under § II, claims 6-9, and amended claims 4 and 21-23, are entitled to the benefit of the filing dates of parent applications 09/206,499 (December 7, 1998) and 08/828,242 (March 31, 1997). Therefore, the claimed subject matter is not obvious over U.S. Patent No. 6,235,477 B1 in view of Kohler et al.

For at least the above reasons, withdrawal of this rejection is requested.

XX. Obviousness-type double patenting over U.S. Patent No. 6,194,385 B1

Claims 2, 4, 5-9, and 22-26 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 4 and 5 of U.S. Patent No. 6,194,385 B1 (hereinafter "the '385 patent"). Applicants request that the requirement for submission of a Terminal Disclaimer with respect to the '385 patent be held in abeyance until such time that there is an indication of allowable subject matter.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at (650) 621-8581.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: Oct. 24, 2003

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Limited Recognition (37 C.F.R. § 10.9(b)) attached
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